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EPIDEMIC CEREBRO-SPINAL MENINGITIS.

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Cerebro-spinal meningitis was first recognized as a definite disease by Vieussieu, in Geneva, in 1805. It is very probable that some of the epidemics in preceding centuries were cerebro-spinal meningitis; but, in the absence of definite clinical reports and the records of post-mortem examinations, it is impossible to be certain of this. The history of these early epidemics and the supposed identity of some of them with cerebro-spinal meningitis has been admirably treated in a paper by Dr. S. G. Webber. After Geneva, the next appearance of the disease was in Medfield, Massachusetts, in 1806, and it was described by Danielson and Mann in the *New England Medical and Agricultural Register.* In the same volume of this magazine there is a letter to the editor from Vincennes, Indiana, describing a virulent epidemic disease there which principally attacked young people, and the editor very pertinently asks if this might not be the same disease as that described by Danielson and Mann.

Apparently beginning in Medfield, Mass., the disease extended as an epidemic over the New England States and into Canada, Pennsylvania, and Maryland, and prevailed until 1816. There are two interesting descriptions of the disease in this period. Elisha North, Goshen, Conn., in 1811 published a small book on spotted fever, in which he not only gave his own experience with the disease, but collected a number of descriptions, many of which had appeared in the newspapers. The other important article relating to this period is the report of a committee appointed by the Massachusetts Medical Society in 1809 to investigate the disease. The committee was composed of James Jackson, Thomas Welch, and J. C. Warren, and in the report there is an account of eight post-mortem examinations, most of which were made by Warren. Danielson and Mann had previously reported the results of four post-mortem examinations.

Hirsch, in his admirable description of the disease, divides it into four periods. The first from 1805 to 1830, in which the disease principally prevailed in the United States; the second from 1837 to 1850, in which it principally prevailed in France, and extended from France into Algiers; third, from 1855 to 1875, when it prevailed chiefly in Germany; and the fourth from 1875 to the present time, in which the disease appears to have been generally diffused, and has appeared in small epidemics in a great number of places.

From 1820, which marks the end of the first period of the epidemic prevalence in the United States, there was but little seen of the disease until 1849, when it prevailed in some troops stationed at New Orleans, and in small epidemics in various places in the South. More or less of it was seen in both armies during the civil war, and a good description is given by Upham, who observed an epidemic in the troops stationed at Newbern, N. C. At the same period the disease prevailed extensively at Philadelphia and in Boston. Since that time there has been a considerable epidemic in Boston in 1874; in Lanaconing, Md., in 1892, and in New York in 1893.

Considered as an epidemic, cerebro-spinal meningitis has many features which distinguish it from epidemics of other infectious diseases. As a rule, none of the epidemics have shown a continuous extension, this being noticeably the case with the first recognized epidemics. In the French epidemics from 1840 to 1845 it appeared in some cases to extend with the movement of troops, and was undoubtedly carried into Algiers in this period by the French troops. As a rule, the outbreaks of the disease have been seen as perfectly isolated epidemics in places which had been hitherto free from it. Almost all of the epidemics have appeared in the winter and spring. Woodward speaks of the disease in Litchfield County as appearing in the spring when the frost was being dissolved and the ground breaking up, and says the disease seemed to be more common in rainy weather. There are few exceptions to this rule. In a few places the disease appeared in the summer.

During the past winter and spring a small epidemic of the disease has prevailed in Boston. We have collected all of the cases which were seen in the Boston City Hospital, the Massachusetts General Hospital, and the Children's Hospital from June, 1896, to October, 1897, and have found 111 cases. In 1896, 1 case appeared in June; 1 case in September; 3 cases in December; in 1897, 1 case in January; 10 in February; 23 in March; 29 in April; 21 in May; 14 in June; 7 in July; and 3 in September.

In general, the disease has been most prevalent in children and young adults.

Lichtenstern, in the epidemic in Cologne in 1885, found that only 23 of the 111 cases occurred after the thirtieth year. The ages given by Lichtenstern for his 111 cases are almost exactly the same as we have found in the same number of cases.

Some writers do not believe that the disease is contagious, and in going over the accounts of the epidemics we have found very little evidence for contagion; as a rule, but single cases have appeared in the same family and in the same house. A map of the city, giving the distribution of the single cases, shows them to be pretty well scattered over the city, there being only two localities where the cases were especially numerous.

In a question of the probability of the transmission of an infectious disease we must consider the location of the disease in the body, and the ways in which the organisms causing it can pass from the lesions of the disease to the outside; further, the viability of the organisms and the possibilty of their leading a saprophytic existence.

The lesions of meningitis are chiefly in the meninges in the brain and cord, and in most cases confined there. In a certain number of cases there are lesions in the lungs, ears, and nose in which large numbers of organisms are present, and from which infection to neighboring objects or persons could easily take place. The organism, as far as we have been able to tell from its behavior on culture-media and in the tissues, has a feeble vitality, and would not be capable of leading a saprophytic existence. It must be remembered, however, that we cannot reproduce the conditions which organisms may find in nature. The organism increases in the affected individual, and, in a certain number of cases, may infect his surroundings, and may, in a manner which we do not know, be conveyed to the tissues of a susceptible individual, and there produce the disease. Why this takes place in some cases and not in others, and the conditions under which it takes place, we do not know.

There is but little in the literature bearing on the subject of immunity in this disease. We have been able to find but five cases in which the same individual is reported to have had the disease twice, and in one of these the second attack is to be considered a relapse and not a fresh infection. The mortality of the 111 cases was 68½ per cent.

A great deal of interest attaches to the sporadic cases of cerebrospinal meningitis. We can only be certain that these sporadic cases represent the same disease as the epidemic form, when the same organism has been found in cultures. So far we have only been able to find one instance in which the diplococcus intracellularis, the organism of epidemic cerebro-spinal meningitis, was found in a sporadic case. In most of these cases no cultures have been made, but, so far as we can judge from the clinical and anatomical descriptions, many of these sporadic cases represent the true epidemic form. Almost all observers who have been acquainted with the epidemic form of the disease speak of the presence of sporadic cases occurring both before and after the epidemics. In the reports of the sporadic cases we think it may be generally assumed that the cases which recovered were of the epidemic form. So far we have not been able to find a case which certainly could be regarded from the accompanying pneumonia or endocarditis as pneumococcus meningitis which has recovered. In the same way there are no recoveries noted from cases of meningitis secondary to thrombosis of the lateral sinuses or disease of the middle ear, in which cases the streptococcus pyogenes is usually the infecting agent. This matter of the relation of sporadic cases to the epidemic form is one of great importance, and can only be determined by careful bacteriological examination of the organs of the cases which die, and bacteriological examination of the exudation obtained by spinal puncture in all cases. It seems probable that sporadic cases of epidemic cerebro-spinal meningitis constantly occur, and under conditions the nature of which we are not aware may so increase in number as to form an epidemic.

Nothing can be learned with regard to these cases from examination of mortality tables. One gets the impression from such tables that the disease is very frequently not recognized when it occurs, and that many cases are reported as meningitis which are not so. A large percentage of the cases of meningitis are reported in such tables as occurring in children under one year of age, whereas all forms of meningitis are extremely rare at this age. In our 111 cases there was but one case under one year.

The etiology of cerebro-spinal meningitis until recently has been involved in obscurity. The first description of an organism which might be considered as the diplococcus intracellularis was given by Lichtenstern in 1885. He found in the exudation in the meninges a few cocci, sometimes single, sometimes in groups similar in arrangement to gonococci, enclosed in white corpuscles. Schwabach found diplococci in the pus-cells in a case of otitis media secondary to meningitis.

The first definite description of the organism was given by Weichselbaum in 1887. The organism is described by him as a diplococcus which, in the lesions, is found almost solely within the cells. He found that it grew best on agar-agar, the pure cultures forming a white, rather viscid growth, and the single colonies often appearing to be formed of small confluent masses. In cultures the organisms grow singly, in pairs, and in tetrads; both in cultures and in the tissue they are decolorized by the Gram stain. Weichselbaum inoculated mice, guinea-pigs, rabbits, and dogs with pure cultures of the organism. Subcutaneous inoculations were without result, but inoculations in the pleural or peritoneal cavities proved fatal in guinea-pigs and rabbits in from one to four days. In these serous membranes, inflammation with sero-fibrinous exudation was produced. He produced meningitis and encephalitis in dogs by inoculating them directly in the meninges. He called the organism the diplococcus intracellularis meningitidis.

There were few confirmations of the discovery of Weichselbaum until 1895. Jäger found the same organism in twelve cases of epidemic cerebro spinal meningitis occurring in the garrison at Stuttgart. His description of the organism agrees essentially with that of Weischselbaum, with the exception that he says a capsule was sometimes found around the organisms, and that cover-slips made from the cultures could be stained with Gram. Weichselbaum claimed that neither in cultures nor in the tissues would the organism take the Gram stain. Since then the organism has been generally found in the epidemics of the disease which have been investigated, and in one sporadic case.

In thirty-five of our cases on which post-mortem examinations were made, diplococci were found in cultures or on microscopic examination of the exudation or in microscopic sections of the tissues in all but four cases. In most of the cases they were found by all three methods of examination. In one case in which they were not found at the post-mortem examination they had previously been found in the fluid withdrawn by spinal puncture. Two of the other cases were very chronic, and no acute lesions were found. The fourth case was a chronic case with a mixed infection with tuberculosis. The diagnosis of the mixed infection of this case was made from the character of the lesions in the meninges and from the extension of the inflammatory exudation along the nerves without any evidence of tubercular lesions, although old tubercles were found in the meninges. In a certain number of cases cultures failed to give the organism, although they were abundantly present, as shown by cover-slip examination of the exudation in the meninges and microscopic sections. As showing the difficulty in growing the organisms in cultures made from the meninges at the post-mortem examination, ten cultures were made in one case from the exudation on the brain, and six from the cord, cover-slip examination showing abundant organisms in the cells. Only two of the cultures from the brain and one from the cord showed a growth, a single colony being found on each tube. In ten cultures from the brain and nine from the cord, in another case, but two tubes showed a growth. As a rule, the organisms were more easily obtained in cultures made in the acute cases than in the chronic. In a few of the cases the culture-tubes showed a very abundant growth of the organism, so abundant that on casual inspection of the tube the growth might very well have been taken for the pneumococcus.

When grown in pure culture the diplococcus intracellularis of Weichselbaum has the following characteristics: It is of about the same size as the ordinary pathogenic micrococci, and appears in diplococcus form as two hemispheres separated by an unstained interval. It stains with any of the ordinary stains for bacteria and is decolorized by the Gram method of staining. There is considerable irregularity in staining, some organisms being brightly stained, others more faintly. Sometimes this difference in staining is seen in a single pair of organisms, one being more brightly stained than the other. There may also be considerable variation in size, the larger organisms staining imperfectly. In these swollen organisms there is often a brightly stained point in the centre, while the remainder of the cell is scarcely colored. This condition may have been mistaken by Jäger for a capsule around the organism. These variations in size and in staining appear to be due to degeneration, and are more common in old than in fresh cultures. Division usually takes place in one plane, giving rise to diplococci; tetrads are occasionally seen. There is little or no tendency to grow in the streptococcus form, although short chains of from four to six organisms may be found. We have never seen the streptococcus form described by Jäger, and in the short chains the longitudinal line on which he lays so much stress was not seen. In cultures the organism does not give a profuse growth on any media. We have found the blood-serum mixture of Löffler the best adapted for its growth. From its feeble growth on agar we are sure that had this medium been generally used for the first cultures, the organism in many instances would not have been found. In all cases a large number of organisms appeared to be dead, or at least they did not grow. Even when a large quantity of an exudation, which on microscopic examination contained large numbers of the organisms, was spread over the surface of a culture-tube, only single colonies developed. The same was true in transplanting colonies. In place of a streak, single colonies developed in the line of the needle. To be sure of obtaining growth it was necessary to make a number of cultures, using large amounts of the exudation. To keep pure cultures going, transfers were made daily, and four or five tubes inoculated. On the Löffler serum mixture the diplococcus forms round, whitish, shining, viscid-looking colonies, with smooth, sharply-defined outlines, and may attain a diameter of 1 to 1½ mm. in twenty-four hours. In acute cases, when large numbers of the organisms are present, there was in some cases an abundant growth of minute, round, transparent colonies bearing much resemblance to the pneumococcus lanceolatus. The growth is feeble on plain agar, better on glycerin agar, though on neither so good as on blood-serum. In bouillon the growth is feeble and the media become only slightly cloudy. At the bottom of the test-tube there is a scanty, whitish sediment which rises up as a viscid string when the tube is shaken.

In the tissues the diplococcus is almost strictly confined to the interior of the polynuclear leucocytes. It was never found in the bodies of other cells. It has no definite position in the cell, and is never found in the nucleus. When smears of an exudation are made, appearances suggestive of this may be found, the result of distortion of the cells in making the preparation. The number of organisms found in the cells varied from a single pair to cells so closely packed with them that the nucleus was obscured. In no case were the diplococci found except in connection with the lesions of the disease. So far as could be learned from cultures of the blood, liver, spleen, and kidneys the organism never produces septicæmia. Mixed infections with other organisms were not uncommon. The pneumococcus was found seven times in connection with the diplococcus intracellularis and once Friedländer's bacillus was found. Terminal infections with staphylococci and streptococci were occasionally found. The results of inoculations are confirmatory of previous experiments. The organism has very feeble pathogenic powers, even when injected into the pleural and peritoneal cavities of rabbits and guinea-pigs. In a small percentage of cases death was produced in from twenty-four to forty-eight hours, and a slight fibrino-purulent exudation was found in the membranes. Typical meningitis was produced in a goat by inoculating directly into the spinal canal. The animal died within twelve hours, and at the post-mortem examination a slight fibrino-purulent exudation was found in the meninges of both the brain and cord.

Lumbar puncture was performed in fifty-five cases, and in a few cases several punctures were made in the same individual. In the fluid obtained the diplococci were found on microscopic examination or in cultures in thirty-eight cases. In seventeen of the cases they were absent. The average duration of time from the onset of disease before spinal puncture was made was seven days in the positive cases, and seventeen days in the negative cases. The longest time after onset in which a positive result was obtained was twenty-nine days. The negative cases were most numerous in the early part of the epidemic before we had realized how difficult it was to obtain cultures of the diplococcus in all cases. In one case in which cultures were made by pouring 1 cc. of the fluid obtained over the slanting surface of the culture media, on one tube one colony developed, three on a second, and none on four others. In another case fifteen tubes were inoculated with the fluid. On two of the tubes there were two, and on one ten colonies of the organism; twelve tubes remained sterile. In this case microscopic examination of the fluid showed considerable numbers of diplococci in pus-cells.

The character of the fluid obtained by spinal puncture varied greatly. In some cases, even when diplococci were found in it, it was almost clear, showing only a slight turbidity when held against a dark background. In most of the cases where the puncture was made early in the disease the fluid was turbid, in some almost like pus, and in twenty-four hours a large sediment formed at the bottom of the tube. The amount of fibrin which formed in the fluid varied.

Interesting results were obtained in those cases in which several spinal punctures were made in the course of the disease. In these cases there was a diminution in turbidity, often accompanied by the absence of organisms in the fluid last withdrawn. In one chronic case, of a marked intermittent character, three punctures were made, one before, one after, and one during an exacerbation. In the fluid obtained by puncture before and after the exacerbation no diplococci were found. The fluid obtained during the exacerbation was more cloudy and contained diplococci. In the fluid obtained in early punctures two or three days after the onset of the disease, almost the only cellular elements were the polynuclear leucocytes. Later the large epithelioid cells of the meninges were found among the pus-cells, often enclosing them. A small number of lymphoid cells were found in many cases, and were numerous in the chronic cases. No ill effects were seen from spinal puncture. Dr. Williams believes that the withdrawal of the exudation may be of positive benefit to the patient. A note in the history of one case says the patient became much quieter and slept after the operation. Too much cannot be said of the importance of the procedure in making the diagnosis of the disease. There should always be a microscopical and bacteriological examination of the fluid obtained in order to ascertain what organism is present. Acute meningitis may be due to a variety of organisms, and it is important to know which is present. This knowledge is certainly useful in making the prognosis, and in the future it may be of importance in the treatment.

The pathological anatomy of acute cerebro-spinal meningitis first began to be carefully studied in the French epidemics from 1840 to 1845. The most careful study of the lesions of the disease has been made by the Germans in the epidemics which have prevailed in various places in Germany from 1865 up to the present time.

We have carefully studied the lesions in the tissues in the thirty-five post-mortem examinations made during the epidemic. In most cases post-mortem examinations were made but a short while after death. When the period was longer most of the bodies had been kept, preceding the examination, in a room cooled by a freezing process to from 32°

to 35° F. At every post-mortem examination where it was possible cultures were made from the brain, cord, heart, lungs, liver, kidneys, and spleen. For general histological purposes, portions of the brain, cord, and other organs were hardened both in Zenker's fluid and in alcohol. For the study of nerve degeneration small pieces of tissues were hardened in Müller's fluid or in formaldehyde, followed by Müller's fluid, before staining in Marchi's solution.

For the study of the distribution of the diplococcus and of the histological changes in the tissues, eosin followed by Unna's alkaline methylene-blue solution was found to give by far the most satisfactory stain. The advantage of Unna's solution, which is more alkaline than Löffler's, is that it stains bacteria and nuclei in tissues hardened in Zenker's fluid, which gives a much more perfect fixation of the tissue elements than either alcohol or sublimate. The tissues were almost exclusively embedded in paraffin. The crystals of corrosive sublimate were removed from the sections after cutting so as to avoid prolonged treatment with iodine, which acts injuriously.

In the cases on which post-mortem examinations were made the duration of illness varied from two days up to seventy-four days. The average duration, leaving out of consideration the very chronic case of seventy-four days, was eleven and one-third days; the time not being taken from the stay of the patient in the hospital, but from the initial symptoms of the disease. The duration was really much less than this for the average number of cases, being greatly increased by seven cases, which were twenty-three, thirty-two, twenty-three, thirty-seven, twenty-nine, thirty, and twenty-six days, respectively. Leaving out these and the seventy-four day case, the average duration was six and one-half days, which can be taken as the average length of time of the acute cases, while twenty-eight and a half days can be considered as an average of the chronic cases, here again leaving out the exceptional case of seventy-four days.

The condition of the body varied in the acute and chronic cases. In the acute cases the body was generally well nourished, and in some there was an abundant development of adipose tissue. The chronic cases presented an almost characteristic appearance; the body being greatly emaciated, the skin pale, the abdomen sunken, and the muscles thin and pale. In one case, which was of six days' duration, there was a decubitus over the sacrum. Evidences of herpes and other skin lesions were not as apparent on post-mortem examination as they were during life. In one case there was a perfectly characteristic hemorrhagic eruption over various parts of the body.

Lesions of the nervous system. The lesions produced by the disease may be divided into those affecting the meninges, those affecting the tissues of the brain and cord, and those affecting the cerebral and spinal nerves. The pathological process in the meninges consists in inflammation with purulent, sero-purulent, and fibrino-purulent exudation. The most marked lesions were found at the base of the brain, extending from the optic commissure backward over the crura, the pons, and the medulla. The meninges of the entire brain area were rarely affected. In the most acute cases, in those dying within two or three days from the onset, the conditions were not so marked as in the more prolonged cases. In these very acute cases there was but little exudation. The bloodvessels of the pia-arachnoid were intensely injected, the large bloodvessels appearing as red lines, and the entire surface of the brain had a pinkish hue, due to injection of the smaller vessels. The exudation appeared in yellowish lines in the sulci along the vessels, and in some cases there was but slight cloudiness. In the more advanced cases, those dying from five to twelve days from the onset, the amount of exudation was much greater, and it contained more fibrin. In the chronic cases in which death took place in from fifteen to thirty days from the acute onset, the appearance of the meninges differed widely from that in the acute. The most marked change was œdema and general thickening of the meninges. There was but little evident exudation, yellowish circumscribed foci scattered here and there in the sulci marking the remains of it. The meninges at the base were opaque, enormously thickened, and there were bands of organized tissue extending from point to point. The inflammation was confined to the pia-arachnoid. The adjoining surface of the dura was smooth, and the vessels were but little injected save in the dura of the cord. There were few lesions in the tissue of the brain and cord apparent to the naked eye, and, without careful microscopic examination, lesions, which must be regarded as among the most important of the disease, would have been overlooked. These lesions of the brain and cord were less marked in the most acute cases. In the more advanced cases the surface of the ventricles had lost its glistening appearance. It was softer, sometimes almost mushy to the touch, and small losses of substance or a more or less ragged or uneven condition of the surfaces were found. The general consistency of the brain was but little altered. It may be somewhat softer to the touch, owing to the dilatation of the ventricles, and there may be œdema. Foci of softening and of hemorrhage were found in the tissues of the brain, but there was no definite abscess formation. The cranial nerves were affected to a greater or less degree in all cases. Those most affected were the second, fifth, seventh, and eighth. The Gasserian ganglia were removed in a number of cases, and in all they were found swollen and softened.

The results of the microscopic examination of the tissues differ according to the acuteness of the process. In the most acute cases, in which there was but slight change to the naked eye, the lesions consisted in purulent infiltration of the meninges. The leucocytes in the exudation were almost exclusively polynuclear. In some places they were closely packed together; in others they were found scattered in a finely granular mass which evidently represented a coagulated albuminous exudation. No eosinophile cells were found in the exudation. In more advanced cases the number of cells was much greater, and they appeared in large masses in the meshes of the tissue. Many of these cells, particularly those in the middle of the masses, were swollen and granular, and the nuclei either stained imperfectly or not at all. There was more fibrin than in the more acute cases. It appeared in masses by itself, or as a delicate network among the pus-cells. In one case it had undergone hyaline metamorphosis in places. It was never present to the same extent as in other forms of meningitis, particularly that produced by the pneumococcus. In addition to the leucocytes there were large cells from two to eight times the diameter of a leucocyte. They were present to some extent in all cases, but very few were found in those most acute. The nuclei of these cells were large and vesicular; the protoplasm stained very faintly and was finely granular. It was difficult to make out the protoplasm of these cells, for they were filled with other cells which they had taken up. Polynuclear leucocytes, often in considerable numbers, were found in these cells. The enclosed leucocytes were most often in a vacuole in the large cell, and a clear space could be seen around the periphery of the enclosed cell. The protoplasm of these enclosed cells gradually disappears, the nucleus breaks up into irregular masses of chromatin, and some large cells were found filled with irregular chromatin fragments. The formation of these large cells from the cells of the connective tissue and from those lining the lymph spaces in the tissue could easily be followed. Numerous nuclear figures were found in such cells. In the chronic cases the exudation was of much slighter extent. The meninges were converted into thick, dense masses of tissue resembling cicatricial tissue containing but few cells. In the place of the abundant exudation in the acute cases, masses of degenerated pus-cells and nuclear detritis were found. In various places there were collections of lymphoid and plasma cells around the vessels. The lesions in the tissue of the brain and cord were interesting on account of their frequency, their general bearing on pathological processes, and from being most marked in the particular form of meningitis which is produced by the diplococcus intracellularis. The lesions were most evident in those cases in which from five to ten days elapsed from the onset of the disease until death. In places there was a circumscribed infiltration of the tissue with pus-cells which extended downward from the infiltration in the meninges. The spaces around the dilated vessels were often filled with pus-cells which extended from here into the surrounding brain tissue. In addition to the infiltration around the vessels, single pus-cells were found in the brain tissue, apparently remote from the areas of infiltration. In two cases there was extensive softening, with purulent infiltration and hemorrhage in the cortex of the cerebellum. In these places the cortex was represented by granular masses scattered among the pus-cells and hemorrhage, and the cells of Purkinje had disappeared or only granular fragments representing them were found. The areas in the white matter which showed macroscopically as hemorrhages, under the microscope appeared as foci of fine hemorrhages with but little infiltration with pus-cells. In one case there was an acute focus of softening with purulent infiltration in the pons just over a thrombus in the basilar artery. In this area the tissue was distinctly broken down, necrotic, and infiltrated with pus. In several of the chronic cases in which there were marked thickening and cellular infiltration of the meninges, the same cellular infiltration was found around the vessels extending into the tissue.

The most interesting changes in the brain concern the neuroglia. The most marked changes were found in the cortex beneath the ventricles and in the neighborhood of the foci of softening. With a low power there was a distinct increase in the cells of the cortex outside of the ganglion cells. The neuroglia cells were swollen; their nuclei were large, clear, vesicular, and contained much chromatin. Around these large nuclei there was a faintly stained irregular mass of granular protoplasm. Many of the cells contained two nuclei, and in places there were groups of four or more nuclei closely clustered together, with a considerable amount of protoplasm around them. In all of these places numbers of nuclear figures were found. They presented the same forms as other multiplying nuclei, and in some cases the spindles and centrosomes were distinct.

For the recognition of these nuclear figures much depends either on the condition of the tissue or the period of the disease. They were numerous in some specimens, while in others in which there was evident proliferation they could be found only after prolonged search. In some of the places where the proliferation was most marked there was some infiltration of the tissue with pus-cells; in others the nuclear figures were found at a distance from such infiltrations and in apparently normal tissues. The greatest increase in the neuroglia was found around the foci of hemorrhage and cellular infiltration in the white matter. In every case proliferative changes in the neuroglia were found in the tissues adjoining the ventricles. Even where the ependymal lining was preserved the cells were closely packed together, the nuclei were large, and proliferation had evidently taken place, but no definite nuclear figures were found.

Marked changes in the neuroglia of the cord were found in but one case. In this the changes were most evident in the gray matter of the cord. These neuroglia changes were accompanied by changes in the connective tissue. The cells of the bloodvessels were swollen, increased in number, and nuclear figures were found in them. In the same field nuclear figures were often found in the neuroglia cells and in the cells around bloodvessels. In the small hemorrhagic foci the walls of the vessels were often found infiltrated with large epithelioid cells, together with lymphoid and plasma cells. A definite formation of connective tissue proceeding from this proliferation around the vessels was not found, save in one chronic case, and in this the process had advanced so far that the steps in the formation of connective tissue could not be followed.

Examination of the ganglion cells showed slight changes in these. These changes consisted in an alteration of the cell granules, accompanied with irregularity in shape, and often atrophy of the body of the cell. In some of the sections which were hardened in Fleming's solution, and in some hardened in Müller's fluid, and subsequently treated by Marchi's method for degeneration, fatty degeneration was found in the cell protoplasm. Diplococci were found in variable numbers in the meninges in the brain and cord, and were less numerous in the cord. They were always most numerous in the acute cases where the exudation was composed almost wholly of pus-cells. Variable numbers were found in the single cells, but cells wholly filled with them, which were so common in the alveoli of the lungs, were rarely found.

The most marked lesions in the nerves were found in the second, sixth, and eighth. Lesions of the optic nerves were due to an extension of the inflammatory process from the meninges. The subdural space of the nerve was dilated, but usually contained no cellular exudation. Just as in the brain, the purulent exudation was found in the pia-arachnoid of the nerve. This was infiltrated with pus, and there were masses of pus-cells in the membrane, chiefly around the retinal artery after this had entered into the nerve sheath. In a longitudinal section of the nerve involving the retina the infiltration could be followed from the meninges of the nerve into the eye. In acute cases the cells in the meninges of the nerves and extending between the nerve bundles were polynuclear leucocytes. In more chronic cases along with the pus-cells there were numerous large epithelioid cells similar to those found in the meninges of the brain. Changes similar to those in the optic nerve were found in the olfactory nerve and the bulb, but the cellular infiltration between the nerve bundles was not so marked in this as in the optic nerve. In both optic and olfactory nerve proliferative changes in the neuroglia, similar to those described in the brain, were found. Sections of the eighth nerve in acute cases showed this to be embedded in a mass of pus, the nerve-sheath softened, broken up, and in places entirely lost. The nerve itself was infiltrated with pus-cells, partly in the form of longitudinal lines, partly as a more diffuse infiltration. In the more chronic cases there were fewer pus-cells, and in place of them lines of epithelioid and plasma cells. The seventh nerve frequently showed as great a degree of infiltration as the eighth. Some infiltration was also found along the third and sixth nerves, but it was not so marked. The fourth nerve was examined in but one case, and showed no infiltration. Longitudinal sections of the fifth nerve, involving the ganglion and some of its branches, showed an intense neuritis on the cerebral side of the ganglion. The single bundles of fibres were widely separated from one another, and between them there was considerable exudation in which there were numbers of pus-cells and epithelioid cells.

Sections of the nerve-roots of the spinal cord showed these affected in every case examined. As a rule, the greatest degree of affection of the nerve-roots was found in that part of the cord where the cellular infiltration was greatest, although in some cases a considerable degree of involvement of the nerve-roots was found with but little cellular infiltration of the meninges. Even in the most acute cases these changes in the nerve-roots of the cord were accompanied by proliferative changes in the peri- and endoneurium. The cells of the bloodvessels were swollen, increased in number, and around the bloodvessels along with the pus-cells there were numbers of large epithelioid and plasma cells. Lymphoid cells were comparatively few in number. The greatest amount of nerve-degeneration, as shown by the Marchi method, was found in the optic nerve in one case, and in the eighth nerve in another. In every case degeneration was found in the spinal nerve-roots and was more marked in the posterior than in the anterior nerve-roots. A minor degree of degeneration was found in the nerves of the cauda equina and in the popliteal nerves. In one of the cases a section treated for degeneration was made through the nerves and muscles of the orbit. All showed more or less marked degenerative changes, the optic and the sixth nerve being most affected. The ocular muscles in the section showed advanced fatty degeneration.

In five cases sections were made of the Gasserian ganglia, and of the spinal ganglia in two cases. In the acute cases the Gasserian ganglia were infiltrated with pus, and masses of ganglion cells were found separated from their connection. Single ganglion cells were found lying free in the exudation. Various degrees of degeneration and even complete destruction of these cells was often found. The spinal ganglia were not affected to the same extent as the Gasserian. All seemed to be somewhat swollen and œdematous, but in some this condition was much more marked than in others. The bloodvessels were injected, the ganglia infiltrated with pus. Sections of the ganglia, including longitudinal section of the nerve-roots in connection with it, showed these to be infiltrated with pus. The rapidity with which these changes in the ganglia can take place was shown in a section of the spinal ganglia of a goat which died not later than twelve hours after inoculation in the spinal canal. In one of the ganglia examined there was a beginning purulent infiltration.

Sections of the eye were examined in two cases, in one of which choroiditis, cloudiness of the cornea, and conjunctivitis were found during life. There was a purulent infiltration of the eye extending from the optic nerve. All of the vessels of the choroid were intensely injected, but there were few hemorrhages and no purulent infiltration. The retina on either side of the optic nerve was broken up and infiltrated with pus. The vitreus was filled with a large amount of pus, made up entirely of polynuclear leucocytes. None of them contained eosinophile granules. The largest mass of this pus was adherent to the iris and retina. The anterior chamber contained a large amount of pus. The tissue of the iris was œdematous and infiltrated with pus-cells. No evidence of proliferation was seen in any of the pigmented cells of the iris or ciliary region. Sections passing through the cornea showed the fibres of this separated, and the tissue contained a great amount of pus-cells lying in the corneal spaces. Diplococci were found in large numbers in the pus-cells in the vitreus and anterior chamber.

The condition of the lung is interesting on account of the relation which has very generally been supposed to exist between epidemic cerebro-spinal meningitis and pneumonia. In thirteen cases there was merely congestion with more or less œdema. In seven cases there was broncho-pneumonia, more marked in the lower posterior portion of the lung. In two cases there was characteristic croupous pneumonia; one in the stage of red hepatization bordering on gray. Pneumococci were found in these cases in cultures and on microscopic examination. In eight cases pneumonia due to the diplococcus intracellularis was found. Nearly all of these cases came from the last part of the epidemic. It is very possible that some of the earlier cases in which the lesions were described simply as broncho-pneumonia were really due to the diplococcus intracellularis. The lung lesions consisted macroscopically of areas of consolidation in various parts of the lung, more particularly in the lower lobe, and they were most numerous beneath the pleural surface. The foci varied in size from a pin's head up to that of a pea, and on section some of them resembled small hemorrhages in the tissue.

In other cases the periphery of the area was distinctly hemorrhagic and the centre opaque and yellowish. In one case the consolidation of the lung was so extensive that it might easily have been regarded as croupous pneumonia, particularly as the pleura over it was covered with a definite fibrinous exudation.

On section, this large area was composed of a number of irregular grayish foci, with softened centres and with hemorrhagic and œdematous tissue between them. The lung tissue in the yellowish centres was frequently broken down, and pus oozed from this. On microscopical examination the central areas showed in most cases a purulent infiltration of the tissue with beginning abscess formation. The alveoli contained large numbers of pus-cells; their walls were infiltrated with pus and in places entirely broken down. The foci of consolidation did not appear to be bronchial in origin. The bronchi in the vicinity often contained pus-cells, but their walls were not infiltrated.

The duration of the disease in the cases in which diplococcus pneumoniæ was found was: in two cases, three days; in two cases, two days; in two cases, fifteen days; in one case, nine days; in one case, twenty-three days, and in one case, seventy-four days. It will be seen from this that the lung complications due to the pneumococcus can take place in almost any period of the disease. In the case of seventy-four days' duration, the lesion in the brain and cord could be regarded as almost completely healed, and the lesions in the lungs were acute. In one case in which, from the history as given by the relatives, the disease was only two days in duration the lesions in the lungs were so advanced that they seemed possibly to antedate those of the brain, providing the history as given by the patient's relatives was correct. Immense numbers of diplococci were found in the pus-cells in the lung. They were most numerous in the cells in the centres of the foci where softening was taking place. In the centre of one of the foci a small branch of the pulmonary artery was found occluded by a thrombus formed of pus-cells containing large numbers of diplococci. It seems probable that this thrombus may have come as an embolus from the meninges, and may have produced an infection of the surrounding tissue.

There was great variation in the size of the spleen. In general it was not much enlarged, and was probably smaller than in most of the acute infectious diseases. In only three cases was it found considerably enlarged. The average weight in the adult cases was 163 gms. The lymphatic glands in the uncomplicated cases were never found enlarged.

The liver presented no change beyond acute degeneration. In two cases extensive acute lesions were found in the kidneys. In one of these the kidney lesions had no connection with the meningitis, but were due to an accompanying infection with diphtheria. In the other case there was an acute hemorrhagic nephritis. In this there was an accompanying acute pericarditis, the organism causing which could not be ascertained. The only lesions found in the kidney which could be properly attributed to the meningitis were acute degenerative lesions which were always present.

The intestinal canal was found normal in every case.

In two cases there was acute pericarditis accompanied in one case with foci of necrosis and purulent infiltration of the myocardium. In several other cases in which the myocardium was examined histologically it was found normal.

Lesions of the skin were found in but one of the cases on which post-mortem examination was made. In this case over the upper and lower extremities, chest, and abdomen, there were numerous small dark purplish spots in the skin, varying in size from a pin's head up to that of a pea. On microscopic examination of these areas there was intense congestion and dilatation of the bloodvessels of the skin, with small and diffuse hemorrhages immediately beneath the epithelium. In some of the larger areas there was some purulent infiltration in the centre. No diplococci were found in these lesions.

With a view of ascertaining the frequency, together with the clinical and anatomical features, of cerebro-spinal meningitis due to other organisms than the diplococcus intracellularis, we have collected a number of cases from the reports of the laboratory for the past five years. Most of these cases come from the Boston City Hospital, but a number of them are from private post-mortem examinations, and the bacteriologic and histological examinations were made at the Sears Pathological Laboratory of the Harvard Medical School.

We have found meningitis apart from the epidemic form to be most commonly caused by the tubercle bacillus, the pneumococcus, and the streptococcus. In one case, the entire history of which is very imperfect, there was a mixed infection with the bacillus pyocyanus and the staphylococcus aureus, and in another case the infection was due to the anthrax bacillus. In most of these cases the meningitis was secondary to infection elsewhere, which fact complicates the clinical history relating to the meningeal symptoms. In ten cases the pneumococcus was found and so associated with the lesions of the disease that it can certainly be regarded as primary. In eight of these cases the meningitis was secondary. In two there was fracture of the base of the skull extending across the temporal bone, the organisms evidently gaining entrance into the meninges from the middle ear. In one there was otitis media with necrosis of the bone, and pneumococci were found in both the pus from the ear and in the meninges. In three the meningitis was secondary to acute croupous pneumonia, and in one to acute fibrinous pericarditis. In one case there was broncho-pneumonia and thrombosis of the longitudinal sinus. In two the thickening of the meninges was primary. No other lesions due to the organism have been found in the body.

The records of the post-mortem examinations show some difference in the amount and distribution of the exudation in the meninges. In one case secondary to acute croupous pneumonia there was only a slight purulent fibrinous exudation over the base of the brain, extending a short distance over the lateral convexity on each side. In another case there was an extensive exudation over the base and over almost the entire surface of the brain. The exudation was usually confined to the meshes of the pia-arachnoid, but in one case it is said to have been both in the membranes and on the surface. The microscopic examination showed considerable difference in the lesions here as compared with the epidemic form. There is a large amount of fibrin present in the exudation. The large cells enclosing numbers of leucocytes which were so prominent in the exudation in the epidemic meningitis were generally absent.

The most marked feature in both the pneumococcus and streptococcus meningitis is the acute endarteritis. The condition is similar in kind to the vascular lesions which have been described in tuberculosis of the meninges. The condition of the circulation in the vessels which were affected could not be ascertained.

In many of them there seemed no other change than an acute inflammation of the wall. In some the lumen was filled with cells, chiefly leucocytes, and in others there was a mass of fibrin and red blood-corpuscles. The inflammatory change consisted essentially in an accumulation of cells between the endothelium, which was generally elevated in festoons, and the elastic lamina. In some places these cell accumulations were so great as to occlude the lumen of the vessel, and in others so slight that they might escape notice. The new cells were principally polynuclear leucocytes, but among them were seen larger cells of an epithelioid character. It was not possible to ascertain the origin of the larger cells in the specimen we have. The muscular coat in most cases was unchanged; in others it was partially invaded by leucocytes.

The clinical history of the eight cases in which meningitis was secondary to other conditions did not throw a great deal of light on the symptoms to be attributed to the meningitis. The symptoms referable to this were complicated with symptoms due to other lesions. Vomiting was found in but four cases. Delirium was less common than in the epidemic cases, and in four cases there was unconsciousness. In one of the cases of pneumonia in which there was an extensive exudation in the meninges there was nothing in the symptoms to point to this.

In general, it may be said that the difference between the clinical history of pneumococcus meningitis as compared with the epidemic form is in the absence or slight development of symptoms in the pneumococcus form which pointed to extensive infection of the meninges of the cord and spinal roots, and extension of the infection along the cranial nerves. At the same time it must be remarked that our observations are not sufficiently numerous to make any extensive generalizations.

In two cases the meningitis was primary. In one case, a well-nourished and well-built child of ten months, the disease began with restlessness, high fever, and vomiting, and the temperature continued high until death, three days after the onset. The other case was that of a child who was taken when six days old with general clonic convulsions, accompanied by a temperature of 104° in the first twelve hours, which afterward dropped to 102°. Death occurred on the second day.

There were eight cases of meningitis due to the streptococcus, and in all the meningitis was secondary to infection elsewhere. In four cases the primary infection was in the ear, and in two of these there was thrombosis of the lateral sinus. In one the meningitis represented an extension to the meninges of erysipelas of the face and scalp. In one case there was acute endocarditis, and in one the meningitis was secondary to an alveolar abscess. One case was of especial interest in showing an infection which doubtless took place from the nose. In this case there was a fracture of the base of the skull extending across the cribriform plate of the ethmoid bone. Pus-cells and streptococci were found in the nose.

In all these cases the lesions in the meninges were very similar to those found in the pneumococcus infection. The exudation was purulent, with a very variable amount of fibrin, usually not so much as in the pneumococcus cases. The acute endarteritis was well marked, and there was no extension of the process into the brain.

The clinical histories of these cases of the streptococcus meningitis do not show anything of especial importance. Opisthotonos was found in but one case, and was not well marked. Pain and stiffness of the neck were found in two cases.

Symptoms referable to the eyes were noted in three cases.

There was one case of meningitis due to the anthrax bacillus. The case was that of a man, about forty years of age, who was a teamster engaged in handling hides. He had a carbuncle on the neck, which was removed by operation. Infection of the alimentary canal probably took place through the instrumentality of his fingers, which he was constantly putting into his mouth to feel an inflamed tooth. At the post-mortem examination there were thirteen carbuncles at various places in the intestinal canal, and an acute hemorrhagic meningitis with focal hemorrhages throughout the brain. The exudation in the meninges was distinctly hemorrhagic, and numerous anthrax bacilli were found in the tissue.

There is no doubt that acute meningitis may be produced by the entrance into the meninges of a number of infectious organisms. These forms are rarely primary. The organisms enter the meninges either by the formation of a communication between the meninges and some cavity where they may be accidentally present (as in the middle ear or nose), or by the extension to the meninges of an infectious process in the vicinity (mastoiditis, erysipelas), or they are brought to the meninges by the blood from some other focus in the body (pneumonia, endocarditis). In tuberculous meningitis we have never found a single case in which the lesions in the meninges could be regarded as primary. The only two cases of apparently primary infection were in the two pneumococcus cases noted, and in one of these the infection may have come from the intestinal canal. We believe that all infections of the meninges other than the diplococcus intracellularis are fatal, but this can only be determined by microscopic and bacteriological examination of the exudation obtained during life by spinal puncture. If tubercle bacilli, pneumococci or streptococci are found with the evidences of meningitis in a case which recovers, it would settle the point; clinical evidence without lumbar puncture will not.

IMPLANTATION OF THE URETERS INTO THE RECTUM IN EXSTROPHY OF THE BLADDER, WITH A DESCRIPTION OF A NEW METHOD OF OPERATION.[1]

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The unsatisfactory character of the results following operations designed for the restoration of the anterior bladder wall in exstrophy of that organ has led surgeons to abandon these procedures. Among the most successful of the flap-operations is that introduced by Dr. Daniel Ayres, the immediate result, when the operation is finally accomplished, being to close the defect with skin-flaps in two layers, the cutaneous surface of one of which is directed toward the mucous membrane of the posterior wall of the bladder, the expectation being that this would finally perform the function, to a greater or less extent, of the normal lining of the bladder-wall. The final outcome of these attempts, in my experience, has been far from satisfactory. The growth of hair upon the vesical surface of the skin-flap which forms the anterior bladder-wall leads to the formation of calculous material and the necessity for further and repeated operative interference.

The constant flow of urine, despite every effort to divert this to an artificial channel opening upon the perineum frequently negatives efforts to obtain healing, whether these are directed toward remedying the defect by simple flap operations of the Ayres type or closure of the accompanying gap in the pubic symphysis, after the manner of Trendelenburg.

Trendelenburg's operation consists of a separation of the sacro-iliac articulation, in order to correct the pelvic bony fissure, and a direct

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[1] Read before the Brooklyn Surgical Society, November 4, 1897.